REMARKS

Claims 2-4, 6-8, 10-28 32 and 33 are pending in the present application. Claims 2 and 10 have been cancelled herein without prejudice to their presentation in another application. Claims 3, 4, 6, 11-13 and 32 have been amended, support for which can be found in the claims and throughout the specification. New claims 34-46 have been added, support for which can be found throughout the specification and the originally filed claims. Upon entry of the present amendment, claims 3, 4, 6-8, 11-28 and 32-46 will be pending.

Applicants have added new claims 34-46, support for which can be found in the originally filed claims and throughout the specification. None of the references of record, alone or in combination, teach or suggest the subject matter recited in new claims 34-46.

As a preliminary matter, Applicants acknowledge receipt of the "Attachment for PTO-948" outlining changes for prosecution of applications containing drawings. To date, however, no Form PTO-948 has been received. Accordingly, the "Attachment for PTO-948" is not relevant in the present application.

I. The Claimed Invention Is Novel

Claims 2-4, 6 and 8 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,371,017 (hereinafter, the "Houghton reference"). Applicants traverse the rejection and request reconsideration in view of the amended claims.

Claim 2 has been cancelled and claims 3, 4 and 6 have been amended to recite "NS4 or NS5." Applicants reserve the right to pursue the cancelled subject matter in another application. The Houghton reference does not teach, nor does the Office Action assert, recombinant nucleic acid molecules comprising a nucleotide sequence encoding hepatitis C virus NS4 or NS5 protein. Thus, the Houghton reference does not teach every feature recited in claims 3, 4, 6 and 8. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

II. The Claimed Invention Is Not Obvious

A. Claims 10-13

Claims 10-13 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the combination of the Houghton reference and Selden, *Curr. Prot. Mol. Biol.*, **1987**, 9.2.1 (hereinafter, the "Selden reference"). Applicants traverse the rejection and request reconsideration in view of the amended claims.

The Office Action asserts that it would have been *prima facie* obvious for one skilled in the art to have resuspended the nucleic acid molecule of the Houghton reference in tris buffered saline of the Selden reference to form a pharmaceutical composition. Although Applicants disagree, the rejection is moot in view of the cancellation of claim 10 and amendment of claims 11-13. Thus, the combination of the Houghton reference and Selden reference does not produce Applicants' claimed invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

B. Claims 6-8, 13 and 14

Claims 6-8, 13 and 14 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the combination of the Houghton and Selden references. Applicants traverse the rejection and request reconsideration in view of the amended claims.

The Office Action asserts that it would have been *prima facie* obvious for one skilled in the art to have used various promoter-enhancer combinations and host cells in expressing the nucleic acid molecule of the Houghton reference. Although Applicants disagree, the rejection is moot in view of the amendment of claims 6 and 13. Thus, the combination of the Houghton reference and Selden reference does not produce Applicants' claimed invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

III. The Claimed Invention Is Enabled

Claims10-28, 32 and 33 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to provide an enabling disclosure. The Office Action mistakenly asserts that it would require

undue experimentation for one skilled in the art to practice the claimed invention as it relates to prophylactic immunization of humans against HCV infection or therapeutic immunization against acquired infection. The reasoning provided in the Office Action is centered around two points -- first, the invention is allegedly drawn to "more than just an immune response" and, second, generation of immune responses in mice is not predictive of humans. Applicants traverse the rejection and request reconsideration because one skilled in the art would be able to practice the claimed invention without being required to perform undue experimentation.

Regarding the first reason, claims 17-28 recite methods of "inducing an immune response against hepatitis C virus in a human..." The claims do not recite methods of inducing a "protective" immune response. The Office Action has improperly tried to restrict Applicants' claimed invention by importing a limitation from the specification into the claims and then hold Applicants' claimed invention is not enabled. The enablement requirement of § 112 is satisfied so long as a disclosure contains sufficient information that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (the legal standard for enablement under § 112 is whether one skilled in the art would be able to practice the invention without undue experimentation). In applying the enablement requirement, the "invention" that must be enabled is that defined by the claims. *Ex parte Erlich*, 3 U.S.P.Q.2d 1011 (Pat. Off. Bd. App. 1987). In *Erlich*, the Patent Office Board of Appeals was presented with a similar set of circumstances. The Examiner had rejected the claims there at issue (which related to processes for using monoclonal antibodies to isolate and purify human fibroblast interferon) because a screening assay step that was not required by the claims allegedly had not been enabled. Significantly, the Board reversed the Examiner's rejection, noting that the appealed claims did not require the assay step:

> The present disclosure as well as that of the parent application does enable one of ordinary skill in the art to practice the claimed invention. Thus, the claims on appeal are disclosed in the manner provided by 35 U.S.C. §112, first paragraph, ... and we reverse this rejection of the claims.

Erlich, 3 U.S.P.Q.2d at 1014. (emphasis in original). As in *Erlich*, Applicants have enabled practice of the claimed methods and compositions. As in *Erlich*, the Examiner's rejection is improper

because it is directed to different methods. Indeed, "protective" is not recited in the claims. That some embodiments of Applicants' specification may recite that the methods provide "protective" immunity is of no moment in regard to the claimed invention. Indeed, any amount of immune response generated by the claimed methods would be beneficial to a human in whom the immune response is generated. In addition, any amount of immune response would be considered by a person skilled in the art to be a therapeutic amount. Indeed, Applicants are not claiming a method of "curing" a hepatitis C infection. Thus, Applicants have enabled the claimed invention.

The Office Action also mistakenly asserts that it would require undue experimentation for one skilled in the art to practice the claimed invention in humans. The Office Action asserts that, despite the data regarding the humoral, cytotoxic, and anti-tumor effects in mice (*see*, Figures 2, 3 and 4 of the specification), the results in mice cannot be extrapolated to humans. The only reasoning provided in support of this assertion is that because mice cannot be infected with HCV, the response to an HCV vaccine in mice cannot be extrapolated to humans. Applicants recognize that mice do not outwardly express the disease state of a hepatitis C virus infection. Mice are, however, capable of eliciting an immune response to HCV, as is shown throughout Applicants' specification. Further, the title of Encke *et al.*, *J. Immunol.*, **1998**, *161*, 4917-4923 (hereinafter, the "Encke reference") itself clearly teaches that mice are, indeed, an animal model for inducing immune responses.

In view of the data regarding the humoral, cytotoxic, and anti-tumor effects of the claimed compositions in mice, one skilled in the art would have no reason to doubt that an immune response would be generated in humans. Applicants remind the Examiner that the claims are not directed to using a mouse model to evaluate the HCV disease state in response to particular compounds. Rather, the claims are directed to methods of inducing an immune response. The Office Action provides no evidence that a human would fail to generate an immune response to the claimed compositions.

Referral in the Office Action to Houghton, *Current Topics in Microbiology and Immunology*, **1999**, pp327-339 (hereinafter, the "Houghton reference") does not support the position taken in the Office Action. The Houghton reference does not teach or suggest that results in mice cannot be extrapolated to humans. Indeed, the Houghton reference refers to studies with mice, guinea pigs, and chimpanzees. The notion that dosages may have to be adjusted from one animal to another

in no way points out the lack of expected success in humans. Further, that efficacy studies are suggested to be carried out in primates, such as chimpanzees, is of no surprise in view of the FDA's requirements for safety and the like. Neither the PTO nor the patent laws, however, are charged with the duties of the FDA. Thus, the Houghton reference does not teach or suggest that the humoral, cytotoxic, and anti-tumor effects of the claimed compositions in mice would not also be expected to be generated in humans.

Further, referral in the Office Action to Chattergoon, *FASEB J.*, **1997**, *11*, 753-763 (hereinafter, the "Chattergoon reference") not only fails to support the positions taken in the Office Action but, in fact, supports Applicants' position. The Office Action asserts that the Chattergoon reference "clearly points out" that there is no evidence of success of using DNA vaccines in humans. In contrast, the Chattergoon reference states:

> The ability of plasmid DNA to induce immune responses after inoculation has been demonstrated in several animal models. Further, within the limits of these disease models, the immune responses elicited by DNA vaccines have been shown to be protective.

(page 762, left column). The only evidence that the Chattergoon reference points out is that there is little evidence that the immune responses will be "completely" protective against any human pathogen. Indeed, as stated above, Applicants' claims neither recite nor require "complete" protective immunity. Rather, Applicants' claims are directed to inducing an immune response. In addition, Table 1 of the Chattergoon reference actually points out that the investigator "Ray" has identified HCV as a target of DNA vaccines by in which "mouse/rat" has been identified as the animal model. Thus, the Chattergoon reference does not support the position taken in the Office Action.

Finally, the statement in the Encke reference referred to in the Office Action also does not support the position taken therein. The Office Action appears to assert that the Encke reference teaches that mice are not predictive of humans. The sentence from the Encke reference referred to in the Office Action states:

> However, the clinical efficacy of DNA-based immunization in generating antiviral immune responses against HCV in humans remains to be established.

(page 4922-4923). Thus, the authors of the Encke reference refer to the "clinical efficacy" of the DNA vaccines, not whether the DNA vaccines will generate an immune response. That a complete protective immune response that is clinically safe can be elicited may indeed remain to be seen. As stated numerous times, however, Applicants' claims are not directed to curing an HCV infection but, rather, recite methods of "inducing an immune response."

In view of the foregoing, there is no reason to believe that one skilled in the art would be required to perform undue experimentation in order to make and use the claimed invention to induce an immune response in humans. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

IV. Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (215) 564-8906 if there are any questions regarding Applicants' claimed inventions. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 2 and 10 have been cancelled.

Claims 3, 4, 6, 11-13 and 32 have been amended and new claims 34-46 have been added as follows:

3. (Amended twice) The recombinant nucleic acid molecule of claim 6 wherein said nucleotide sequence encodes a fusion protein encoding [NS3, NS4, or NS5,] NS4 or NS5 or any combination thereof.

4. (Amended twice) The recombinant nucleic acid molecule of claim 6 wherein said nucleotide sequence encodes a fragment of at least 50 amino acids of [nonstructural protein selected from the group consisting of NS3, NS4, and NS5] NS4 or NS5.

6. (Amended twice) A recombinant nucleic acid molecule comprising a nucleotide sequence encoding [a] hepatitis C virus [nonstructural] NS4 or NS5 protein wherein said nucleotide sequence is operably linked to a promoter, enhancer, polyadenylation sequence, and optionally 5' UTR of hepatitis C virus.

11. (Amended twice) The pharmaceutical composition of claim 13 wherein said nucleotide sequence encodes a fusion protein encoding [NS3, NS4, or NS5,] NS4 or NS5 or any combination thereof.

12. (Amended twice) The pharmaceutical composition of claim 13 wherein said nucleotide sequence encodes a fragment of at least 50 amino acids of [nonstructural protein selected from the group consisting of NS3, NS4, and NS5] NS4 or NS5.

13. (Amended twice) A pharmaceutical composition comprising:

a) a recombinant nucleic acid molecule comprising a nucleotide sequence encoding [a] hepatitis C virus [nonstructural] NS4 or NS5 protein, wherein said nucleotide sequence is operably linked to regulatory elements functional in human cells; and

b) a pharmaceutically acceptable carrier or diluent;

wherein said regulatory elements functional in human cells comprise a promoter, enhancer, polyadenylation sequence, and optionally 5' UTR of hepatitis C virus.

32. (Amended twice) A method of treating a human who is infected with hepatitis C virus comprising administering to said human a pharmaceutical composition [of claim 13] in an amount effective to induce a therapeutic immune response against hepatitis C virus, wherein said composition comprises a recombinant nucleic acid molecule comprising a nucleotide sequence encoding a hepatitis C virus nonstructural protein, wherein said nucleotide sequence is operably linked to regulatory elements functional in human cells, and a pharmaceutically acceptable carrier or diluent, wherein said regulatory elements functional in human cells comprise a promoter, enhancer, polyadenylation sequence, and optionally 5' UTR of hepatitis C virus.

34. (New claim) A recombinant nucleic acid molecule comprising a nucleotide sequence encoding a hepatitis C virus NS3 protein, wherein said nucleotide sequence is operably linked to a promoter, enhancer, polyadenylation sequence, and the entire 5' UTR of hepatitis C virus or a fragment thereof including the last nine nucleotides of the hepatitis C virus 5' UTR.

35. (New claim) The recombinant nucleic acid molecule of claim 34 wherein said nucleotide sequence encodes a fusion protein encoding NS3 or a combination of NS3 with NS4 or NS5, or a combination of NS3 with both NS4 and NS5.

36. (New claim) The recombinant nucleic acid molecule of claim 34 wherein said nucleotide sequence encodes a fragment of at least 50 amino acids of NS3.

37. (New claim) The recombinant nucleic acid molecule of claim 34 wherein said promoter is a cytomegalovirus promoter and said enhancer is a Rous Sarcoma Virus enhancer.

38. (New claim) A recombinant host cell comprising a nucleic acid molecule of claim 34.

39. (New claim) A pharmaceutical composition comprising:

a) a recombinant nucleic acid molecule comprising a nucleotide sequence encoding hepatitis C virus NS3 protein, wherein said nucleotide sequence is operably linked to regulatory elements functional in human cells; and

b) a pharmaceutically acceptable carrier or diluent;

wherein said regulatory elements functional in human cells comprise a promoter, enhancer, polyadenylation sequence, and the entire 5' UTR of hepatitis C virus or a fragment thereof including the last nine nucleotides of the hepatitis C virus 5' UTR.

40. (New claim) The pharmaceutical composition of claim 39 wherein said nucleotide sequence encodes a fusion protein encoding NS3 or a combination of NS3 with NS4 or NS5, or a combination of NS3 with both NS4 and NS5.

41. (New claim) The pharmaceutical composition of claim 39 wherein said nucleotide sequence encodes a fragment of at least 50 amino acids of NS3.

42. (New claim) The pharmaceutical composition of claim 39 wherein said promoter is a cytomegalovirus promoter and said enhancer is a Rous Sarcoma Virus enhancer.

43. (New claim) The pharmaceutical composition of claim 39 further comprising a facilitator.

44. (New claim) The pharmaceutical composition of claim 43 wherein said facilitator is bupivacaine.

45. (New claim) A pharmaceutical composition comprising:

a) a recombinant nucleic acid molecule comprising a nucleotide sequence encoding a hepatitis C virus nonstructural protein, wherein said nucleotide sequence is operably linked to regulatory elements functional in human cells;

b) a pharmaceutically acceptable carrier or diluent; and

c) a facilitator;

wherein said regulatory elements functional in human cells comprise a promoter, enhancer, polyadenylation sequence, and optionally 5' UTR of hepatitis C virus.

46. (New claim) The pharmaceutical composition of claim 45 wherein said facilitator is bupivacaine.